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EXAMINER	
MERTZ, PREMA MARIA	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,370	DREANO ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-25,28,31-50 and 53-58* is/are pending in the application.

4a) Of the above claim(s) *33-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-25, 28, 31-32, 40-50, 53-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/19/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 19-25, 31-37, 40-50, 53-58; species IL-6) on 2/28/2008 is acknowledged. The traversal is on the ground(s) that the restriction is improper because the present invention discloses a method where a low dose of IL-6 is administered (see page 28, lines 8-9 which defines 0.1 mcg/kg to 10 mcg/kg to be low dose and 100 mcg/kg to 500 mcg/kg to be high dose), while Kovalovich discloses administering 1 mcg/g (which is 1000 mcg/kg; page 26606, last sentence of right column) IL-6, which would even be higher than the defined high dose range in the present application. Applicants therefore argue that accordingly, Kovalovich does not negate the special technical feature in the present invention which defines a contribution over the prior art. However, contrary to Applicants arguments, Applicants are arguing limitations not present in the claims and therefore the method described in the reference meets the limitations of Group I. Since the first claimed invention lacks a special technical feature, the other claimed inventions cannot share a special technical feature with the first claimed invention. The methods of Groups 1-4 are patentably distinct from each other because each recites method steps not required by the other, each method uses different starting materials and patient populations and the search of all methods in one patent application would result in an undue search burden.

The Groups as delineated in the restriction requirement 1/28/2008 are patentably distinct one from the other such that each invention could, by itself, in principle, support its own separate patent (as shown by the arguments put forth in the written restriction requirement).

The requirement is still deemed proper and is therefore made FINAL.

Claims 38-39 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 19-25, 28, 31-32, 40-50, 53-58 are drawn to the elected species and are under consideration by the Examiner.

Claim Rejections - 35 USC § 112, first paragraph, scope of enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2a. Claims 19-25, 28, 31-32, 40-50, 53-58, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing proliferation of hepatocytes in CCl4 induced chemical cirrhosis, does not reasonably provide enablement for a method for treating liver injury as recited in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn very broadly to methods of treating all liver injury. The specification, page 1, lines 17-32 and page 2, lines 1-2 recites:

"Liver damage or injury may have diverse causes. It may be due to viral or bacterial infections, alcohol abuse, immunological disorders, or cancer, for example.

Viral hepatitis, due to Hepatitis B virus and Hepatitis C virus, for example, are poorly managed diseases that afflict large number of people worldwide. The number of species of hepatitis viruses known is constantly increasing. Apart from Hepatitis B and C virus, at least four other viruses causing virus-associated hepatitis have been discovered so far, called Hepatitis A, D, E and G-Virus.

Sometimes, substances which are normally non-toxic can become hepatotoxic when abused, such as acetaminophen (APAP) overdoses and ethanol.

Alcoholic liver disease is another widespread disease associated with chronic consumption of alcohol. Immune hepatitis is a rare autoimmune disease that is poorly managed. Liver injury also includes damages of the bile ducts. Primary biliary cirrhosis (PBC) is an autoimmune liver disease characterized by destruction of the intrahepatic bile ducts.

Recently liver injury was found to be a side effect of gene therapy, e.g. acute hepatocellular injury characterized by centrilobular hepatocyte necrosis is a major side effect of viral-based gene therapies targeted to the liver."

However, other than Examples 1-3, pages 26-31, which demonstrate that administration of IL-6 enhances the physiological response to a major parenchymal loss by inducing a massive proliferation of mature hepatocytes when both high and low doses (except 10 mcg/kg) are employed, the specification fails to provide any guidance for the successful treatment of all the other possible liver injuries by administering IL-6.

The specification delimits the instant method to administering IL-6 for the treatment of CCl4 induced chemical cirrhosis of the liver. However, with respect to claims 19-25, 28, 31-32, 40-50, 53-58, as recited, what is claimed in the instant invention broadly encompasses a method of administering "all" types of liver injury by administering IL-6.

By application of the factors set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) quantity of experimentation, (2) guidance presented, (3) the predictability of the art, and (4) the breadth of the claims, in the instant application, the quantity of experimentation to determine which types of liver injury are encompassed by the scope of the claims is practically infinite and the guidance provided in the specification very little, thereby rendering the results of the methods taught in the specification unpredictable (see pages 26-31). Therefore, it would require undue experimentation to determine which types of liver injury, would be encompassed by the scope of the method claims. The disclosure of using IL-6 to treat chemical induced cirrhosis is clearly insufficient support under the first paragraph of 35 U.S.C. 112 for claims, which encompass a method of treating all types of liver injury with IL-6 . In In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), the Courts have held that:

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this

dominance by claims which are insufficiently supported and hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that the scope of the claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Therefore, there are substantial scientific reasons to doubt the scope of enablement, as set forth above. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe treatment of any other liver cirrhosis other than CCl4 induced liver cirrhosis and since it is deemed to constitute undue experimentation to determine all the other types of liver injuries that could be treated with IL-6, the disclosure is not commensurate with the scope of the claims. It is suggested that by employing conventional claim language, the method claims be amended to include the specific condition supported by the instant specification.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as

originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Given the inherent unpredictability of physiological activity, which would include biological processes, i.e., methods of treatment, a certain amount of enablement beyond mere assertion must be required.

The CAFC decision (Genentech Inc. v. Novo Nordisk, 42 USPQ2d 1001, 1997) expressly states that:

"When there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

In the instant case, a method of treating liver injury caused by damages of bile ducts or liver injury which is a side effect of gene therapy, is very different from a method of treating liver cirrhosis caused by CCl4. Furthermore, the limited results presented for treatment of liver cirrhosis caused by CCl4, are not sufficient to enable the

breadth of the claims and are not predictive of in vivo efficacy for treatment of all the other types of liver injuries. Thus, it would require undue experimentation on the part of the skilled artisan to use the claimed method for treated as recited, in the absence of sufficient information to predict the results with an adequate degree of certainty. In view of this unpredictability in the treatment of different liver injuries in which more than regenerating hepatocirrhotic parenchyma is required, there cannot be said to be any reasonable expectation of success at the in vivo application of a potential therapy, especially in view of the fact that the current specification as filed presents no working examples pertaining to the method of treatment of the various liver injuries in vivo. Therefore, a method of treating all liver injuries by administration of IL-6 as recited in claim 1 has not been enabled by the specification. The recitation of "liver injury" in claim 1, is not commensurate with the scope of the specification. Given the breadth of claim 1 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of skill in the art to practice the claimed invention.

Claim rejections-35 U.S.C. 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 19-25, 28, 31-32, 40-50, 53-58, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is rejected as vague and indefinite for several reasons.

Claim 19, line 3, is vague and indefinite because it recites "low dose". The metes and bounds of the claim are unclear because "low" is a relative term.

Claim 19, line 2, is improper because it recites "preventing" which is non-elected subject matter. Appropriate correction is required.

Claim 19 is also vague and indefinite because it recites "liver injury" rather than the condition to be treated.

Claim 19 is vague and indefinite because it is a method claim but fails to recite steps in the method.

Claim 40 is rejected as vague and indefinite for several reasons.

Claim 40, lines 3-4, is vague and indefinite because it recites "low dose". The metes and bounds of the claim are unclear because "low" is a relative term.

Claim 40, line 2, is improper because it recites "preventing" which is non-elected subject matter. Appropriate correction is required.

Claim 40, lines 6-7, is improper because it recites "an expression vector" which is non-elected subject matter. Appropriate correction is required.

Claim 40, line 9, is improper because it recites "cell producing the same" which is non-elected subject matter. Appropriate correction is required.

Claim 40 is also vague and indefinite because it recites "liver injury" rather than the condition to be treated.

Claim 40 is vague and indefinite because it is a method claim but fails to recite steps in the method.

Claim 41 is rejected as vague and indefinite for several reasons.

Claim 41, line 3, is vague and indefinite because it recites "low dose". The metes and bounds of the claim are unclear because "low" is a relative term.

Claim 41, line 2, is improper because it recites "preventing" which is non-elected subject matter. Appropriate correction is required.

Claim 41, line 8, is improper because it recites "an expression vector" which is non-elected subject matter. Appropriate correction is required.

Claim 41 is also vague and indefinite because it recites "liver injury" rather than the condition to be treated.

Claim 41 is vague and indefinite because it is a method claim but fails to recite steps in the method.

Claim 43, line 3, is vague and indefinite because it recites "end stage liver insufficiency". The metes and bounds of the term are unclear. It is suggested that the claim be amend to recite the specific "liver insufficiency" for which there is a basis in the instant specification.

Claim 45, line 3, is vague and indefinite because it recites "acute liver insufficiency". The metes and bounds of the term are unclear. It is suggested that the claim be amend to recite the specific "liver insufficiency" for which there is a basis in the instant specification.

Claim 55 is rejected as vague and indefinite for several reasons.

Claim 55, line 3, is vague and indefinite because it recites "low dose". The metes and bounds of the claim are unclear because "low" is a relative term.

Claim 55, line 6, is improper because it recites "an expression vector" which is non-elected subject matter. Appropriate correction is required.

Claim 41 is also vague and indefinite because it fails to recites "liver injury" rather than the condition to be treated.

Claim 41 is vague and indefinite because it is a method claim but fails to recite steps in the method.

Claims 20-25, 28, 31-32, 42, 44, 46-50, 53-54, 56-58 are rejected as vague and indefinite insofar as they depend on the above rejected claims for their limitations.

Claim rejections-35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4a. Claims 19-22, 28, 31-32, 40-42, 43, 45, 50, 53-54, 55-58, are rejected under 35 U.S.C. 102(b) as being anticipated by Kovalovich et al. (2001)

Kovalovich et al discloses a method of treating liver injury by administration of IL-6 which protects against Fas-mediated death in the liver of mice by establishing a critical level of anti-apoptotic hepatic proteins FLIP, Bcl-2 and Bcl-xL (see abstract; see Figure 1, page 26606). The recitation of the term "liver injury" in the claims encompasses liver injury by the Fas agonist, Jo-2 monoclonal antibody (see page 26606, column 2, first full paragraph, first 6 lines). Therefore, the method described in the

reference meets the limitations of instant claims 19-22, 28, 31-32, 40-42, 43, 45, 50, 53-54, 55-58.

4b. Claims 19, 28, 31-32, 40-41, 43-48, 50, are rejected under 35 U.S.C. 102(b) as being anticipated by Selzner et al. (1999)

Selzner et al discloses a method of treating liver injury caused by ischemia and major hepatectomy by administration of IL-6 to mice (see abstract; see Figure 1, page 471; Figure 2, page 471). The recitation of the term "liver injury" in the claims encompasses liver injury ischemia. Therefore, the method described in the reference meets the limitations of instant claims 19, 28, 31-32, 40-41, 43-48, 50.

Conclusion

Claims 19-25, 28, 31-32, 40-50, 53-58 are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For

more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Prema Mertz/
Primary Examiner
Art Unit 1646